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September 24, 1992

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INIT

Attn: Section 8(e) Coordinator (CAP Agreement)

Re: CAP Agreement Identification No. 8ECAP-0110

Dear Sir or Madam:

Union Carbide Corporation ("Union Carbide") herewith submits the following report pursuant to the terms of the TSCA §8(e) Compliance Audit Program and Union Carbide's CAP Agreement dated August 14, 1991 (8ECAP-0110). This report describes a dermal teratology study (rabbits) with diethylene glycol monomethyl ether (DEGME; CASRN 111-77-3).

"Diethylene Glycol Monomethyl Ether (DEGME): Dermal Teratology Study", Dow Chemical U.S.A., December 10, 1984.

A complete summary of this report is attached.

Previous TSCA Section 8(e) or "FYI" Submission(s) related to this substance are:

(None)

Previous PMN submissions related to this substance are: (None)

⑤

This information is submitted in light of EPA's current guidance. Union Carbide does not necessarily agree that this information reasonably supports the conclusion that the subject chemical presents a substantial risk of injury to health or the environment.

In the attached report the term "CONFIDENTIAL" may appear. This precautionary statement was for internal use at the time of issuance of the report. Confidentiality is hereby waived for purposes of the needs of the Agency in assessing health and safety information. The Agency is advised, however, that the publication rights to the contained information are the property of Union Carbide.

Yours truly,



William C. Kuryla, Ph.D.  
Associate Director  
Product Safety  
(203/794-5230)

WCK/cr

Attachment (3 copies of cover letter, summary, and report)

## SUMMARY

DIETHYLENE GLYCOL MONOMETHYL ETHER (DEGME):  
DERMAL TERATOLOGY STUDY IN RABBITS<sup>1</sup>

By:

J. A. John, B. H. Scortichini, T. K. Jeffries,  
N. M. Berdasco and J. F. Quast

Reviewed By:

K. S. Rao

December 10, 1984

Mammalian and Environmental Toxicology Research Laboratory  
Health and Environmental Sciences, USA  
Dow Chemical U.S.A.  
Midland, Michigan 48640

<sup>1</sup>Sponsored by U.S. area glycol ether producers under the auspices of the  
Chemical Manufacturers' Association.

## SUMMARY

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### SUMMARY

Diethylene glycol monomethyl ether (DEGME) was applied to the shaved skin of pregnant rabbits on days 6 through 18 of gestation in order to assess the fetotoxic and teratogenic potential by the dermal route. Groups of 25 bred rabbits were treated with 0 (control), 50, 250 or 750 mg/kg/day of DEGME, and the 29-day fetuses were examined for external, soft tissue and skeletal alterations. Topical application of the highest dose, 750 mg/kg/day, produced slight embryotoxicity, fetotoxicity and toxicity in the maternal animal. Maternal effects were characterized by decreased weight gain and a concurrent physiologic decrease in RBC and PCV values. In addition, a slight increase in embryonic resorptions was observed. The fetal alterations observed, mild forelimb flexure, slight-to-moderate dilation of the renal pelvis, retrocaval ureter, cervical spurs, and delayed ossification of the skull and sternebral bones are considered to be indicative of fetotoxicity but not teratogenicity. Slight fetotoxicity in the form of delayed ossification of the skull and cervical spurs was seen in the 250 mg/kg/day dose group. No adverse maternal, embryonic or fetal effects were observed at 50 mg/kg/day.

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SUMMARY

Diethylene glycol monomethyl ether (DEGME) was applied to the shaved skin of pregnant rabbits on days 6 through 18 of gestation in order to assess the fetotoxic and teratogenic potential by the dermal route. Groups of 25 bred rabbits were treated with 0 (control), 50, 250 or 750 mg/kg/day of DEGME, and the 29-day fetuses were examined for external, soft tissue and skeletal alterations. Topical application of the highest dose, 750 mg/kg/day, produced slight embryotoxicity, fetotoxicity and toxicity in the maternal animal. Maternal effects were characterized by decreased weight gain and a concurrent physiologic decrease in RBC and PCV values. In addition, a slight increase in embryonic resorptions was observed. The fetal alterations observed, mild forelimb flexure, slight-to-moderate dilation of the renal pelvis, retrocaval ureter, cervical spurs, and delayed ossification of the skull and sternebral bones are considered to be indicative of fetotoxicity but not teratogenicity. Slight fetotoxicity in the form of delayed ossification of the skull and cervical spurs was seen in the 250 mg/kg/day dose group. No adverse maternal, embryonic or fetal effects were observed at 50 mg/kg/day.

## INTRODUCTION

Diethylene glycol monomethyl ether (DEGME) is a colorless liquid used as a solvent for various resins, lacquers, paints, dyes, inks, and cosmetics. DEGME is low in acute oral toxicity; the single-dose oral LD50 was reported by Smyth et al. (1941) to be 9.21 g/kg for rats (50% aqueous solution). The single-dose oral LD50 value for rabbits is 7.19 g/kg (Rowe and Wolf, 1981). Diethylene glycol monomethyl ether is not appreciably irritating to the skin of rabbits (Wolfe, 1954). The skin absorption LD50 in rabbits is reported to be about 20 ml/kg (Browning, 1965).

A probe study was conducted to establish the maximum tolerated dose level of DEGME via dermal application in pregnant rabbits (John et al., 1983). Undiluted DEGME (specific gravity = 1.021) was applied to the back (clipped free of hair) of New Zealand White rabbits at dose levels of 100, 300 and 1000 mg/kg/day (approximately 0.1, 0.3 and 1.0 ml DEGME/kg of body weight) on days 6 through 18 of gestation. Ten inseminated rabbits were used per dose group. A group of 10 control rabbits received distilled water at a dose volume of 1.0 ml/kg on the same gestation days. The backs of all rabbits were covered with an occlusive bandage consisting of absorbent gauze (controls only), non-absorbent cotton, and cloth held in place with adhesive tape. All rabbits were sacrificed on day 19 of gestation and gross observations of the uterine contents and internal organs were made.

Dermal application of 1000 mg/kg/day of DEGME produced evidence of toxicity in pregnant rabbits. Three animals died or were sacrificed in a moribund condition. Surviving animals in this group lost weight during the treatment period and showed decreased ingesta in the intestinal tract, decreased adipose tissue in the abdominal cavity or gastric lesions due to inanition. Evidence of embryotoxicity was observed in the 1000 mg/kg/day group as well; the incidence of implantations undergoing resorption was considerably higher than controls (46% vs 4% in controls) though the small group sizes precluded identification of a difference using statistical procedures. No evidence of maternal or embryonal toxicity was observed in rabbits given 100 or 300 mg/kg/day of



DEGME dermally. No evidence of irritation to the skin at the application site was observed upon gross examination of any of the treated rabbits.

The objective of the study reported herein was to assess the teratogenic potential of DEGME following dermal application, a likely route of human exposure to this chemical. The New Zealand White rabbit was chosen as a test species based on historical use within this laboratory, the acceptability of methods to apply the test chemical by the dermal route (Ouellette et al., 1983), and the known sensitivity of this species to the fetotoxicity and teratogenicity of other glycol ethers (Hanley et al., 1982). Based on the results of the probe study where 1000 mg DEGME/kg/day was severely toxic to the pregnant doe and the embryo, dose levels of 50, 250, and 750 mg/kg/day were selected for the definitive teratology study.

#### MATERIALS AND METHODS

Test Material. Diethylene glycol monomethyl ether (Lot #MM830303) was obtained from the Dow Chemical Company. The test material was analyzed by the Quality Assurance Dept., Dow Chemical Company, on September 28, 1983, and was found to be 99.6% pure by gas chromatography. The sample was reanalyzed on 12/20/83 and reported to be 99.2% pure.

Test Animals. Stock supplies of male and female New Zealand White rabbits (Langshaw Farms, Augusta, Michigan) were obtained. Animals were housed singly in wire-bottomed cages in rooms designed to control temperature at approximately 22° C, relative humidity at approximately 50% and photocycle at 12 hours light and dark. Animals were acclimated to the laboratory<sup>1</sup> for at least two weeks prior to breeding. Female rabbits (approximately 3.5-4.5 kg) were artificially inseminated (Gibson et al., 1966); the day of artificial insemination was considered as day zero of gestation.

<sup>1</sup>Fully accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC).

Randomization of test animals, grouped according to their day zero of gestation, was performed using computer-generated tables of random numbers. All animals were uniquely identified by metal ear tags. Food (Certified Laboratory Rabbit Chow No. 5322, Ralston Purina Company, St. Louis, Missouri) and municipal tap water were available ad libitum. Analysis of Purina Certified Chow was performed by the Ralston Purina Company to confirm that the diets provide adequate nutrition, and to quantify the levels of selected contaminants associated with the formulation process; results were maintained in the Mammalian and Environmental Toxicology Research Laboratory. Analysis of tap water (municipal water supply) was performed according to the Standard Operating Procedures of the Mammalian and Environmental Toxicology Research Laboratory.

Experimental Design and Test Material Application. Groups of 25 inseminated rabbits were treated with 50, 250, or 750 mg/kg/day of DEGME, applied dermally, on days 6 through 18 of gestation. Control animals were treated with distilled water. The dose volume of undiluted DEGME was 0.05, 0.25 or 0.75 ml/kg for the 50, 250, or 750 mg/kg/day dose levels, respectively. Control animals were treated with distilled water at 0.75 ml/kg of body weight. The methods of application of the test material and occlusion of the application site were similar to those developed by Ouellette et al. (1983).

A section (approximately 10 x 15 cm) on the back of each rabbit was clipped free of hair with electric clippers on day 0 of gestation. On day 6 of gestation, a piece of non-absorbent cotton was placed over the dosing area on the back. A cloth bandage over the cotton was held in place with adhesive tape. Control rabbits had absorbent gauze between the skin and nonabsorbent cotton. Rabbits remained in bandages throughout the dosing period (days 6 through 18 of gestation). All animals were dosed under the bandage daily, with bandages being replaced as needed during the treatment period. On day 19 of gestation, the bandages were removed and the area of application was wiped to remove any residue of test material. Dosing of the test animals started on January 9, 1984; the last group of rabbits were submitted for cesarean section on February 29, 1984.

Maternal Observations. Animals were observed daily throughout the experimental period for indications of toxicity from the test material. Animals found dead or moribund were submitted for gross pathologic examination. Body weights were recorded daily throughout the dosing period and on days 19 and 29 of gestation. Statistical analysis of body weight and body weight gain was performed using data recorded on gestation days 6, 9, 12, 15, 19 and 29. In addition, maternal liver weights were recorded at the time of cesarean section. Sections of maternal skin from the application site and an untreated site, liver, spleen and bone marrow were preserved in neutral phosphate buffered 10% formalin for possible histological examination; no histologic examinations were made on these tissues. At cesarean section, blood was collected from the test rabbits for hematologic evaluation. The evaluation included red blood cell (RBC) count, hemoglobin concentration (HGB), packed cell volume (PCV), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelet count, and total white blood cell (WBC) count (ELT-8, Ortho Instruments, Westwood, MA).

Fetal Observations. Test animals were sacrificed by carbon dioxide inhalation on day 29 of gestation. The uterine horns were exteriorized through a midline incision in the abdominal wall and the following data were recorded: 1) number and position of fetuses in utero, 2) number of live and dead fetuses, 3) number and position of resorption sites, 4) the number of corpora lutea, 5) the sex, body weight and crown-rump length of each fetus, and 6) any gross external alteration. The uteri of apparently nonpregnant animals were stained with a 10% solution of sodium sulfide (Kopf et al., 1964) and examined for evidence of implantation sites. One-half of each litter, selected using a table of random numbers (Steel and Torrie, 1960), were examined immediately by dissection under a low power microscope for evidence of soft tissue alterations (Staples, 1974). All fetuses were then preserved in alcohol, eviscerated and subsequently cleared and stained with alizarin red-S (Dawson, 1926) and examined for skeletal alterations.

Statistical Evaluation. Body weights, absolute and relative organ weights and hematologic parameters were evaluated by Bartlett's test for equality of variance. Statistical outliers were identified by a sequential outlier test (Grubbs, 1969), but were not excluded from analysis. Based upon the outcome of Bartlett's test, a parametric or nonparametric analysis of variance (ANOVA) was performed. If the ANOVA was significant, analysis by Dunnett's test or the Wilcoxon Rank-Sum test with Bonferroni's correction (Steel and Torrie, 1960) was also performed.

Statistical evaluation of the frequency of pre-implantation loss, resorptions among litters and the fetal population, and fetal alterations was made by a censored Wilcoxon test (Haseman and Hoel, 1974) with Bonferroni's correction. Pregnancy rates were analyzed by the Fisher exact probability test (Siegel, 1956).

The nominal alpha levels used are as follows:

Bartlett's Test for Variance	$\alpha=0.01$
Analysis of Variance	$\alpha=0.10$
Dunnett's Test	$\alpha=0.05$ two-sided
Wilcoxon Rank-Sum Test	$\alpha=0.05$ two-sided, with Bonferroni correction (Miller, 1966)
Fisher's Test	$\alpha=0.05$ one-sided
Modified Wilcoxon Test	$\alpha=0.05$ one-sided

Because numerous measurements were statistically compared in the same group of animals, the overall false positive rate (Type I errors) is much greater than the cited alpha levels would suggest. Thus, the final interpretation of numerical data considered statistical analyses along with other factors such as dose-response relationships and whether the results were significant in the light of other biologic and pathologic findings.

## RESULTS

Maternal Observations. One rabbit in the 750 mg/kg/day group exhibited a slight redness to the skin in the scapular area which was apparently caused by rubbing of the bandage as the animal moved. No clinical signs

of toxicity from the test material were observed during the course of treatment. Evidence of slight maternal toxicity was observed in rabbits to which 750 mg/kg/day of the test material was applied. Pregnant rabbits gained slightly less weight than controls throughout the period of dosage, days 6 through 18 of gestation, and the weight gain in this group was statistically identified as different from control during gestation days 9 through 11 (Table 1). Pregnant rabbits in this high dose group showed a depression of red blood cell counts and packed cell volume (Table 1). One female in the 750 mg/kg/day group and one in the 50 mg/kg/day group died during the course of treatment (Table 2), and each was found to have a hairball in the stomach. These deaths are considered to be unrelated to treatment. One other high dose female died during the experimental period and no specific cause of death was determined upon gross necropsy. No indications of treatment-related maternal toxicity were seen in the middle or low dose groups.

Embryo- or Fetotoxicity. Reproductive parameters, pregnancy rate, implantations per dam, resorption rate, litter size, and fetal body measurements were not statistically identified as different from control values, though the incidence of embryonic resorptions was slightly higher in the 750 mg/kg/day group than the concurrent control incidence (Table 2).

Fetal Observations. Evidence of fetotoxicity was observed in the high dose group where the observations of mild forelimb flexure, slight to moderate dilation of the renal pelvis, retrocaval ureter, cervical spur and delayed ossification of the hyoid bone and sternebral bones occurred at a higher incidence than controls as indicated by a censored Wilcoxon Test (Table 3). These are considered to be minor changes indicative of fetal toxicity, but not of teratogenicity. Among fetuses in the 250 mg/kg/day group, the incidences of only 2 minor skeletal changes, delayed ossification of the hyoid bone and occurrence of cervical spurs, were increased as compared to control. No indications of fetotoxicity were seen at 50 mg DEGME/kg/day.

## DISCUSSION

Topical application of DEGME produced a fetotoxic response at 750 mg/kg/day, a dose level which was slightly toxic to the maternal animals. The alterations observed in the fetuses, mild forelimb flexure, slight to moderate dilation of the renal pelvis, retrocaval ureter, cervical spurs, and delayed ossification of skull and sternebral bones, have been observed as background variants in this species in our laboratory (Table 4), and are considered by other teratologists to be "minor" anomalies which occur spontaneously (Palmer, 1968, 1972, 1977; Stadler et al., 1983; R. E. Staples, personal communication, 1984). Thus, the increased incidence of these minor anomalies at 750 mg/kg/day is considered to be indicative of fetotoxicity, but not teratogenicity. Dilations of the renal pelvis and delayed ossification are considered to be indicative of delayed fetal development in this species.

The high dose, 750 mg/kg/day, produced slight maternal toxicity in this study, as evidenced by reduced weight gain during pregnancy, particularly during the dosage period, and slight hematologic changes. Though these changes are not considered severe, data from the probe study (John et al., 1983) suggests that this dose approaches a maximum tolerated dose. In the probe study, dermal application of 1000 mg/kg/day resulted in death or morbidity in 3 of 10 adult rabbits, and evidence of embryo-lethality. - In the current teratology study, embryo resorption was slightly increased in the 750 mg/kg/day group. Application of 250 mg DEGME/kg/day produced slight fetotoxicity as evidenced by an increase in two minor skeletal alterations.

In conclusion, the results of this study show that dermal application of DEGME to pregnant rabbits at 750 mg/kg/day produces slight toxicity in the maternal animal and embryo, and causes fetotoxicity in the absence of teratogenicity. Dermal application of 250 mg DEGME/kg/day produces slight fetotoxicity. These effects were not observed at 50 mg DEGME/kg/day.

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TITLE OF STUDY: DIETHYLENE GLYCOL MONOMETHYL ETHER (DEGME):  
DERMAL TERATOLOGY STUDY IN RABBITS

In compliance with FDA and EPA Good Laboratory Practice Regulations, the study phases were inspected by the Quality Assurance Unit and the results of these inspections reported to Management and the Study Director on the dates listed below. The report accurately reflects the data generated in accordance with the regulations and standard operating procedures of the laboratory. All data and the reports are located at the submitting laboratory.

Study Started: <u>9 Jan 1984</u>	Report Issued Date: <u>10 Dec 1984</u>
Dates of Inspection: <u>16 Dec 1983</u>	Date of Report: <u>16 Dec 1983</u>
<u>3 Feb 1984</u>	<u>3 Feb 1984</u>
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Table 1

DEGME: DERMAL TERATOLOGY STUDY IN RABBITS

Body Weights, Organ Weights and Hematologic Parameters of Pregnant Rabbits

		Dose Level, mg/kg/day			
		0	50	250	750
Number of dams		23	23	24	21
Maternal body weight on gestation day <sup>a</sup>					
	6	3980±258	3875±228	3931±304	3955±244
	9	3958±258	3823±227	3914±289	3929±256
	12	3993±247	3860±233	3933±299	3908±284
	15	4047±281	3925±266	3984±299	3913±338
	19	4056±334	3976±272	4043±320	3867±442
	29	4213±345	4152±297	4174±299	4077±454
Maternal body weight gain on gestation days <sup>a</sup>					
	6-9	-22±48	-52±70	-17±65	-26±57
	9-12	34±70	36±53	19±52	-21±95*
	12-15	54±67	66±61	50±97	5±137
	15-19	6±115	51±62	60±80	-46±183
	19-29	157±115	176±83	131±131	210±183
	6-19	76±174	101±95	112±142	-88±297
Total	6-29	233±226	277±125	243±208	122±353
Maternal liver weight on gestation day 29					
	Absolute <sup>a</sup>	110.03±16.22	115.51±19.85	114.05±16.87	119.60±26.03
	Relative <sup>b</sup>	2.62±0.40	2.77±0.38	2.72±0.29	2.92±0.55
Hematologic parameters measured on day 29 <sup>c</sup>					
	RBCx10 <sup>6</sup> /mm <sup>3</sup>	5.79±0.48	5.60±0.51	5.80±0.38	5.39±0.61*
	HGB (g/dl)	12.3±0.9	12.2±1.0	12.5±0.8	11.6±1.3
	PCV (%)	43.7±3.1	42.8±3.7	44.0±2.6	40.8±4.5*
	MCV (μ <sup>3</sup> )	76±2	76±2	76±2	76±2
	MCH (μg)	21.3±0.9	21.9±1.0	21.5±0.9	21.6±1.0
	MCHC (%)	28.2±0.7	28.6±0.9	28.3±0.8	28.5±0.7
	Platx10 <sup>3</sup> /mm <sup>3</sup>	373±94	354±91	341±79	369±126
	WBC x10 <sup>3</sup> /mm <sup>3</sup>	5.5±2.1	5.2±1.5	5.4±2.1	5.4±1.5

<sup>a</sup>Grams, mean ± S.D.

<sup>b</sup>Grams organ weight/100 grams body weight, mean ± S.D.

<sup>c</sup>Mean ± S.D.

\*Different from control value by Dunnett's test, α = 0.05.

Table 2

DEGME: DERMAL TERATOLOGY STUDY IN RABBITS

Observations Made at the Time of Cesarean Section of Inseminated Rabbits

	Dose Level, mg/kg/day			
	0	50	250	750
Number of females bred	25	25	25	25
Number of maternal deaths	0	1	0	2
Pregnancies detected by stain	0/2	0/1	0/1	1/2
% Pregnant, total <sup>a</sup>	92 (23/25)	96(24/25)	96(24/25)	96 (24/25)
Number of litters	23	23	24	21
Corpora lutea/dam <sup>b</sup>	10±2	9±2	10±2	10±2
Implantation sites/dam <sup>b</sup>	8±4	9±2	9±2	9±2
% Pre-implantation loss <sup>c</sup>	15±23	6±8	9±9	14±19
Fetuses/litter <sup>b</sup>	7±4	8±3	8±3	6±3
Resorptions/litter <sup>b,d</sup>	1.3±1.9	1.0±1.4	1.3±2.2	3.3±3.8
% Implantations resorbed <sup>d</sup>	15 (29/190)	12(24/199)	14(31/225)	37(69/189)
% Litters with resorptions <sup>d</sup>	61 (14/23)	57(13/23)	58(14/24)	86 (18/21)
Litters totally resorbed <sup>d</sup>	2	1	1	3
Resorptions/litters with resorptions <sup>d</sup>	2.1 (29/14)	1.8 (24/13)	2.2 (31/14)	3.8 (69/18)
Dead fetuses	0	0	0	0
Sex Ratio, M:F, %	54:46	51:49	44:56	52:48
Fetal body weight, g	38.2±6.1	37.6±4.5	34.9±5.5	34.3±5.2
Fetal crown-rump length, mm	91.1±5.7	90.0±4.4	90.2±5.8	87.2±6.8

<sup>a</sup>Number of females pregnant by visual inspection of the uterus at the time of cesarean section and at the time of necropsy or after staining the uterus with sodium sulfide stain.

<sup>b</sup>Mean ± S.D.

<sup>c</sup>Percent per litter, mean ± S.D.

<sup>d</sup>Implantations detected by sodium sulfide stain were not included in these calculations.

<sup>e</sup>Mean of litter means ± S.D.

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TABLE 3

DEGME: DERMAL TERATOLOGY STUDY IN RABBITS

Incidence of Fetal Alterations Among Litters of Rabbits

		<u>Dose Level, mg/kg/day</u>			
		<u>0</u>	<u>50</u>	<u>250</u>	<u>750</u>
		Number of Fetuses (Number of Litters) Examined			
External Examination		161(21)	175(22)	194(23)	120(18)
Soft Tissue Examination		91(21)	93(22)	104(23)	68(18)
Skeletal Examination		161(21)	175(22)	194(23)	120(18)
		Percent Affected (Number Affected)			
<u>External Observations</u>					
Forelimb flexure - mild	F <sup>a</sup>	2(3)	1(1)	2(3)	24(29)*
	L	14(3)	5(1)	13(3)	61(11)
Forelimb flexure - severe <sup>†</sup>	F	0	0	1(2)	1(1)
	L	0	0	4(1)	6(1)
Anonychia <sup>†</sup>	F	0	0	0	1(1)
	L	0	0	0	6(1)
<u>Soft Tissue Observations</u>					
Dilated renal pelvis	F	0	0	0	12(8)*
	L	0	0	0	28(5)
Retrocaval ureter	F	0	0	0	9(6)*
	L	0	0	0	22(4)
Convolutured ureter	F	2(2)	0	0	1(1)
	L	10(2)	0	0	6(1)
Hydronephrosis and dilated ureter <sup>†</sup>	F	0	0	0	1(1)
	L	0	0	0	6(1)
Mineralized deposits in kidney	F	0	2(2)	0	0
	L	0	9(2)	0	0
Pale spleen	F	0	0	0	4(3)
	L	0	0	0	11(2)

TABLE 3 (Cont'd)

DEGME: DERMAL TERATOLOGY STUDY IN RABBITS

Incidence of Fetal Alterations Among Litters of Rabbits

		Dose Level, mg/kg/day			
		0	50	250	750
Segmented spleen	F	0	0	0	1(1)
	L	0	0	0	6(1)
Undersized spleen	F	0	0	0	1(1)
	L	0	0	0	6(1)
Accessory Spleen	F	0	0	0	1(1)
	L	0	0	0	6(1)
Strangulated hepatic tag	F	1(1)	0	0	0
	L	5(1)	0	0	0
Hydrocephaly <sup>†</sup>	F	1(1)	0	0	0
	L	5(1)	0	0	0
Undersized left carotid <sup>†</sup>	F	0	0	1(1)	0
	L	0	0	4(1)	0
Ventricular septal defect <sup>†</sup>	F	0	1(1) <sup>b</sup>	0	0
	L	0	5(1)	0	0
Agenesis of gall bladder <sup>†</sup>	F	0	1(1) <sup>b</sup>	0	0
	L	0	5(1)	0	0
Retrosophageal right subclavian artery	F	0	1(1) <sup>b</sup>	0	0
	L	0	5(1)	0	0
Horseshoe Kidney <sup>†</sup>	F	0	1(1) <sup>b</sup>	0	0
	L	0	5(1)	0	0
<u>Skeletal Observations</u>					
Skull					
-hyoid, delayed ossifi- cation	F	8(13)	11(19)	29(57)*	58(70)*
	L	43(9)	27(6)	83(19)	89(16)
-hyoid, crooked	F	1(2)	1(2)	1(1)	2(2)
	L	5(1)	9(2)	4(1)	6(1)

TABLE 3 (Cont'd)

DEGME: DERMAL TERATOLOGY STUDY IN RABBITS

Incidence of Fetal Alterations Among Litters of Rabbits

		Dose Level, mg/kg/day			
		0	50	250	750
-parietal bone, delayed ossification	F	0	1(1)	0	0
	L	0	5(1)	0	0
Vertebrae -hemivertebra <sup>†</sup>	F	0	0	1(1)	1(1)
	L	0	0	4(1)	6(1)
-cervical spur	F	0	2(3)	9(17)*	8(10)*
	L	0	14(3)	35(8)	33(6)
-lumbar spur	F	5(8)	4(7)	5(9)	3(4)
	L	19(4)	23(5)	26(6)	17(3)
-axis, extra site of ossification	F	1(1)	1(1)	1(1)	0
	L	5(1)	5(1)	4(1)	0
-axis, delayed ossification	F	0	0	0	2(2)
	L	0	0	0	11(2)
-atlas, delayed ossification	F	0	0	0	1(1)
	L	0	0	0	6(1)
-cervical centra, delayed ossification	F	0	0	0	1(1)
	L	0	0	0	6(1)
-scoliosis with fused ribs <sup>†</sup>	F	0	0	1(1) <sup>C</sup>	0
	L	0	0	4(1)	0
Ribs -forked <sup>†</sup>	F	0	0	1(2) <sup>C</sup>	1(1)
	L	0	0	9(2)	6(1)
-calloused	F	0	1(1)	0	0
	L	0	5(1)	0	0
-slightly calloused	F	0	1(1)	0	0
	L	0	5(1)	0	0
-irregular pattern of ossification	F	0	1(1)	0	0
	L	0	5(1)	0	0

TABLE 3 (Cont'd)

DEGME: DERMAL TERATOLOGY STUDY IN RABBITS

Incidence of Fetal Alterations Among Litters of Rabbits

		Dose Level, mg/kg/day			
		0	50	250	750
-extra (detached) rib in thoracic area	F	1(1)	0	0	0
	L	5(1)	0	0	0
Sternebrae -delayed ossification	F	46(74)	33(58)	45(88)	78(93)*
	L	90(19)	82(18)	87(20)	100(18)
-extra site of ossification	F	0	0	0	1(1)
	L	0	0	0	6(1)
-fused	F	1(2)	2(3)	2(3)	3(3)
	L	10(2)	14(3)	13(3)	17(3)
Other -thumb digit, delayed ossification	F	0	0	0	3(3)
	L	0	0	0	6(1)

<sup>a</sup>F= fetuses; L = litters

<sup>b</sup>One fetus in the 50 mg/kg/day group exhibited a ventricular septal defect, agenesis of the gall bladder, retroesophageal right subclavian artery, and a horseshoe kidney.

<sup>c</sup>One fetus in the 250 mg/kg/day group exhibited 2 forked ribs and 2 fused ribs associated with scoliosis.

<sup>†</sup>Considered to be a malformation.

\*Different from control value by a censored Wilcoxon test,  $\alpha=0.05$ .



TABLE 4

NEW ZEALAND WHITE RABBITS

Incidence of Fetal Malformations in Historical Control Population<sup>a</sup>  
in the Dow Toxicology Research Laboratory

		Cumulative Total # Affected/# Examined	Range of Individual Study Incidences
Forelimb flexure	F <sup>b</sup>	17/5891	0/199-6/220
	L	14/750	0/26-4/27
Anonychia	F	1/5891	0/199-1/170
	L	1/750	0/26-1/24
Dilated renal pelvis	F	8/2591	0/109-2/117
	L	6/749	0/24-2/27
Dilated ureter	F	0/2591	--
	L	0/749	--
Ventricular septal defect	F	6/2591	0/109-2/96
	L	6/749	0/24-2/19
Agenesis of gall bladder	F	1/2591	0/109-1/96
	L	1/749	0/24-1/19
Horseshoe kidney	F	0/2591	--
	L	0/749	--
Hemivertebra	F	6/5666	0/197-2/178
	L	6/727	0/26-2/23
Scoliosis	F	0/5666	--
	L	0/727	--
Forked ribs	F	7/5666	0/197-1/120
	L	7/727	0/26-1/14
Fused ribs	F	8/5666	0/197-1/116
	L	8/727	0/26-1/16
Delayed ossification of hyoid	F	94/5666	0/197-46/198
	L	40/727	0/26-17/23
Cervical spurs	F	12/5666	0/197-9/198
	L	8/727	0/26-5/23

<sup>a</sup>Includes data from vehicle control groups from 42 studies conducted between 1974 and 1984. Routes of exposure include drinking water, oral gavage and inhalation.

<sup>b</sup>F = fetuses; L = litters.

DIETHYLENE GLYCOL MONOMETHYL ETHER (DEGME):  
DERMAL TERATOLOGY STUDY IN RABBITS<sup>1</sup>

APPENDIX TABLES

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<sup>1</sup>Sponsored by U.S. area glycol ether producers under the auspices of  
The Chemical Manufacturers' Association.

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NOTE: Individual animal data, along with means and standard deviations, are presented in appendix tables. No statistical analyses are reflected in these tables.

TABLE A-1

1-1

DEGME: DERMAL TERATOLOGY STUDY IN RABBITS

INDIVIDUAL AND MEAN BODY WEIGHT VALUES OF PREGNANT RABBITS

DOSE LEVEL: 0 MG/KG/DAY

MATERNAL BODY WEIGHT (G)  
DAY(S) OF GESTATION

ANIMAL NUMBER	DAY 6	DAY 9	DAY 12	DAY 15	DAY 19	DAY 29
=====	=====	=====	=====	=====	=====	=====
84A0001	3837.5	3778.8	3803.0	3824.3	3712.8	3868.1
0002	4031.5	3999.5	4032.0	4062.0	4101.0	4096.1
0003	3782.3	3760.6	3773.4	3760.5	3336.0	3356.8
0004	3895.0	3835.9	3883.8	3893.2	3933.2	4321.0
0011	3592.2	3597.3	3681.8	3735.8	3772.0	4012.0
0012	3664.9	3660.4	3714.0	3756.2	3854.7	4085.8
0021	3921.0	3883.0	4095.6	4130.0	4209.0	4253.0
0022	3864.4	3805.0	3835.8	3882.2	3746.1	3988.4
0031	4167.0	4113.0	4120.0	4209.0	4221.0	4401.0
0032	3938.7	3975.0	4080.0	4207.0	4330.0	4714.6
0042	4247.0	4235.0	4332.0	4202.0	4154.0	4407.9
0043	4024.0	4122.0	4039.5	4130.0	4142.0	4295.2
0044	4579.6	4598.7	4446.0	4688.8	4799.0	4750.0
0051	3915.0	3884.7	3955.6	3985.6	4033.0	4233.0
0052	4432.0	4344.0	4361.0	4452.0	4520.0	4790.1
0061	3955.1	3977.9	3990.5	----	4117.8	4254.6
0071	4007.0	3897.6	3940.7	3988.4	3961.5	3999.2
0072	4139.0	4086.4	4091.0	4197.4	4234.0	4309.0
0081	3815.4	3787.9	3809.6	3878.3	3941.0	4139.4
0083	3715.7	3751.5	3780.8	3857.1	3866.9	4044.0
0093	3986.3	4023.0	4094.0	4145.8	4208.9	4344.0
0095	4416.0	4373.0	4461.0	4536.7	4576.4	4643.0
0096	3617.0	3552.7	3511.0	3511.0	3522.0	3592.0
MEAN	3980.2	3958.4	3992.7	4047.0	4056.2	4213.0
S.D.	257.5	257.7	247.1	281.2	334.0	344.9

TABLE A-1(CONTINUED)

1-2

DEGME: DERMAL TERATOLOGY STUDY IN RABBITS  
INDIVIDUAL AND MEAN BODY WEIGHT VALUES OF PREGNANT RABBITS

DOSE LEVEL: 50 MG/KG/DAY

MATERNAL BODY WEIGHT (G)  
DAY(S) OF GESTATION

ANIMAL NUMBER	DAY 6	DAY 9	DAY 12	DAY 15	DAY 19	DAY 29
*****	*****	*****	*****	*****	*****	*****
84A0005	3769.0	3703.8	3811.0	3880.0	3948.3	4084.5
0006	3763.6	3714.6	3690.3	3631.0	3625.6	3813.0
0013	3731.3	3886.3	3884.4	3855.7	3958.3	4060.0
0014	4145.6	4059.4	4102.0	4166.5	4244.7	4443.6
0023	3742.8	3658.0	3704.6	3760.0	3885.6	4024.0
0024	4055.0	3996.4	4011.0	4197.2	4234.0	4466.0
0026	3706.6	3610.0	3665.8	3692.8	3709.0	3893.5
0033	4335.7	4125.0	4351.8	4493.5	4412.0	4631.0
0034	3746.4	3676.6	3741.0	3888.0	3812.5	4031.8
0045	3878.9	3807.3	3869.4	3950.7	4010.0	4248.0
0046	4132.2	4119.0	4133.0	4222.0	4375.9	4638.4
0053	3761.1	3675.0	3741.0	3757.1	3838.9	4029.0
0054	4096.9	3973.7	3993.1	3998.5	4169.0	4472.0
0064	3690.0	3696.4	3736.0	3740.0	3748.2	4087.8
0065	3635.0	3536.7	3545.2	3561.0	3557.7	3596.2
0066	4080.0	4005.0	3960.5	4081.9	4104.0	4263.0
0073	4429.3	4498.0#	4497.0#	4624.3#	4689.1	4785.5
0084	3707.9	3676.6	3684.8	3743.0	3851.6	4156.0
0085	3698.4	3690.0	3725.0	3786.4	3844.1	3898.8
0086	3640.0	3607.0	3646.8	3768.4	3830.0	3904.0
0097	3883.9	3787.1	3814.9	3928.2	3963.0	4044.0
0098	3777.8	3746.6	3748.3	3823.7	3848.0	3962.5
0099	3726.8	3685.1	3714.5	3731.0	3797.7	3961.0
MEAN	3875.4	3823.2	3859.6	3925.3	3976.4	4151.9
S.D.	227.6	226.9	233.3	266.2	272.2	296.8

TABLE A-1(CONTINUED)

1-3

DEGME: DERMAL TERATOLOGY STUDY IN RABBITS

INDIVIDUAL AND MEAN BODY WEIGHT VALUES OF PREGNANT RABBITS

DOSE LEVEL: 250 MG/KG/DAY

MATERNAL BODY WEIGHT (G)  
DAY(S) OF GESTATION

ANIMAL NUMBER	DAY 6	DAY 9	DAY 12	DAY 15	DAY 19	DAY 29
=====	=====	=====	=====	=====	=====	=====
84A0007	3578.8	3614.9	3655.6	3483.0	3540.0	3702.0
0008	3798.9	3745.2	3759.0	3765.5	3945.0	4200.0
0015	4059.9	4234.0	4269.0	4084.0	4381.0	4360.0
0016	3898.4	3828.2	3732.7	3744.2	3845.1	3921.0
0027	3630.4	3618.3	3658.0	3793.0	3820.0	4141.0
0028	3802.0	3828.5	3741.6	3974.0	3994.8	4184.0
0035	3600.0	3636.7	3674.1	3721.0	3756.3	3913.0
0037	3793.6	3795.5	3815.9	3961.0	3981.0	4123.0
0038	3970.6	3941.4	3900.4	4086.0	4136.0	4348.3
0047	4517.7	4464.9	4475.2	4463.0	4479.9	4457.5
0048	4088.4	3981.0	3952.3	3868.8	3729.2	3854.7
0055	3904.0	3828.5	3863.2	3961.2	3964.6	4142.0
0067	4493.0	4480.0	4509.9	4575.6	4658.4	4760.9
0068	3703.9	3671.9	3594.5	3714.8	3687.5	3665.0
0075	4157.0	4100.0	4167.9	4221.0	4335.0	4619.6
0076	4205.0	4110.0	4150.0	4215.0	4256.7	4500.0
0077	4359.5	4257.0	4364.0	4369.7	4418.6	4151.0
0078	3541.0	3602.0	3641.0	3682.6	3752.0	3950.4
0087	3815.0	3808.4	3828.9	3927.0	3963.6	4161.0
0088	4187.0	4198.7	4254.0	4349.7	4490.1	4621.8
0089	3666.6	3748.7	3816.5	3847.4	3908.3	4056.9
0100	3582.0	3530.0	3632.0	3676.9	3681.8	3977.1
1994	4348.1	4312.0	4337.5	4448.2	4513.0	4523.0
1995	3643.8	3603.0	3607.9	3671.8	3800.4	3844.5
MEAN	3931.0	3914.1	3933.4	3983.5	4043.3	4174.1
S.D.	303.8	288.8	299.4	299.3	320.0	298.6

TABLE A-1(CONTINUED)

1-4

DEGME: DERMAL TERATOLOGY STUDY IN RABBITS  
INDIVIDUAL AND MEAN BODY WEIGHT VALUES OF PREGNANT RABBITS

DOSE LEVEL: 750 MG/KG/DAY

MATERNAL BODY WEIGHT (G)  
DAY(S) OF GESTATION

ANIMAL NUMBER	DAY 6	DAY 9	DAY 12	DAY 15	DAY 19	DAY 29
=====	=====	=====	=====	=====	=====	=====
84A0009	4083.9	4131.0	4204.0	4315.7	4294.4	4533.5
0010	3735.5	3764.2	3735.6	3603.0	3920.8	4002.0
0017	3890.8	3826.4	3877.3	3879.6	3942.0	4144.0
0018	3771.4	3781.6	3685.0	3470.7	3144.0	3516.0
0019	3885.8	3895.8	3801.0	3976.4	3898.6	4206.0
0020	3756.8	3780.0	3835.9	3946.5	3972.5	4380.0
0029	4021.0	3994.8	4163.3	4184.0	4307.0	4512.0
0030	3755.4	3762.5	3679.9	3783.0	3813.0	4187.0
0039	4253.0	4234.0	4170.0	4152.0	4265.0	4437.7
0040	4182.8	4215.0	4310.0	4350.0	4392.2	4727.3
0049	4549.1#	4524.0	4576.5	4641.9	4592.5	4750.0
0057	3770.7	3718.3	3775.2	3680.3	3314.0	3892.8
0058	3720.0	3684.0	3718.8	3678.8	3523.0	3664.3
0059	3951.3	3845.3	3817.7	3837.0	3944.0	4076.8
0070	3871.7	3903.0	3724.3	3462.0	3204.0	2964.1
0079	3827.6	3646.3	3690.9	3733.0	3906.4	3980.4
0080	4046.0	4033.0	3901.0	3966.6	3969.2	3960.8
0091	4476.6	4478.3	4439.0	4417.0	4336.7	4354.0
0092	3685.3	3641.0	3556.2	3420.0	3080.0	3266.0
1996	3779.4	3743.5	3704.0	3615.0	3351.0	3841.2
1997	4035.0	3908.0	3701.0	4055.9	4034.0	4218.0
MEAN	3954.7	3929.0	3907.9	3912.8	3866.9	4076.9
S.D.	243.6	255.6	283.9	338.3	441.5	454.1

----No Data.

#Indicates statistical outliers which are not excluded from calculations.

TABLE A-2

2-1

DEGME: DERMAL TERATOLOGY STUDY IN RABBITS

INDIVIDUAL AND MEAN BODY WEIGHT GAIN VALUES OF PREGNANT RABBITS

DOSE LEVEL: 0 MG/KG/DAY

MATERNAL BODY WEIGHT GAIN (G)

DAY(S) OF GESTATION

ANIMAL NUMBER =====	DAYS 6-9 =====	DAYS 9-12 =====	DAYS 12-15 =====	DAYS 15-19 =====	DAYS 19-29 =====	DAYS 6-19 =====	DAYS 6-29 =====
84A0001	-58.7	24.2	21.3	-111.5	155.3	-124.7	30.6
0002	-32.0	32.5	30.0	39.0	-4.9	69.5	64.6
0003	-21.7	12.8	-12.9	-424.5	20.8	-446.3	-425.5
0004	-59.1	47.9	9.4	40.0	387.8	38.2	426.0
0011	5.1	84.5	54.0	36.2	240.0	179.8	419.8
0012	-4.5	53.6	42.2	98.5	231.1	189.8	420.9
0021	-38.0	212.6	34.4	79.0	44.0	288.0	332.0
0022	-59.4	30.8	46.4	-136.1	242.3	-118.3	124.0
0031	-54.0	7.0	89.0	12.0	180.0	54.0	234.0
0032	36.3	105.0	127.0	123.0	384.6	391.3	775.9
0042	-12.0	97.0	-130.0	-48.0	253.9	-93.0	160.9
0043	98.0	-82.5	90.5	12.0	153.2	118.0	271.2
0044	19.1	-152.7	242.8	110.2	-49.0	219.4	170.4
0051	-30.3	70.9	30.0	47.4	200.0	118.0	318.0
0052	-88.0	17.0	91.0	68.0	270.1	88.0	358.1
0061	22.8	12.6	----	----	136.8	162.7	299.5
0071	-109.4	43.1	47.7	-26.9	37.7	-45.5	-7.8
0072	-52.6	4.6	106.4	36.6	75.0	95.0	170.0
0081	-27.5	21.7	68.7	62.7	198.4	125.6	324.0
0083	35.8	29.3	76.3	9.8	177.1	151.2	328.3
0093	36.7	71.0	51.8	63.1	135.1	222.6	357.7
0095	-43.0	88.0	75.7	39.7	66.6	160.4	227.0
0096	-64.3	-41.7	0.0	11.0	70.0	-95.0	-25.0
MEAN	-21.8	34.3	54.2	6.4	156.8	76.0	232.8
S.D.	47.8	69.7	67.2	115.3	114.6	173.5	226.2



TABLE A-2 (CONTINUED)

2-2

DEGME: DERMAL TERATOLOGY STUDY IN RABBITS

INDIVIDUAL AND MEAN BODY WEIGHT GAIN VALUES OF PREGNANT RABBITS

DOSE LEVEL: 50 MG/KG/DAY

MATERNAL BODY WEIGHT GAIN (G)

DAY(S) OF GESTATION

ANIMAL NUMBER =====	DAYS 6-9 =====	DAYS 9-12 =====	DAYS 12-15 =====	DAYS 15-19 =====	DAYS 19-29 =====	DAYS 6-19 =====	DAYS 6-29 =====
84A0005	-65.2	107.2	69.0	68.3	136.2	179.3	315.5
0006	-49.0	-24.3	-59.3	-5.4	187.4	-138.0	49.4
0013	155.0	-1.9	-28.7	102.6	101.7	227.0	328.7
0014	-86.2	42.6	64.5	78.2	198.9	99.1	298.0
0023	-84.8	46.6	55.4	125.6	138.4	142.8	281.2
0024	-58.6	14.6	186.2	36.8	232.0	179.0	411.0
0026	-96.6	55.8	27.0	16.2	184.5	2.4	186.9
0033	-210.7	226.8	141.7	-81.5	219.0	76.3	295.3
0034	-69.8	64.4	147.0	-75.5	219.3	66.1	285.4
0045	-71.6	62.1	81.3	59.3	238.0	131.1	369.1
0046	-13.2	14.0	89.0	153.9	262.5	243.7	506.2
0053	-86.1	66.0	16.1	81.8	190.1	77.8	267.9
0054	-123.2	19.4	5.4	170.5	303.0	72.1	375.1
0064	6.4	39.6	4.0	8.2	339.6	58.2	397.8
0065	-98.3	8.5	15.8	-3.3	38.5	-77.3	-38.8
0066	-75.0	-44.5	121.4	22.1	159.0	24.0	183.0
0073	68.7	-1.0	127.3	64.8	96.4	259.8	356.2
0084	-31.3	8.2	58.2	108.6	304.4	143.7	448.1
0085	-8.4	35.0	61.4	57.7	54.7	145.7	200.4
0086	-33.0	39.8	121.6	61.6	74.0	190.0	264.0
0097	-96.8	27.8	113.3	34.8	81.0	79.1	160.1
0098	-31.2	1.7	75.4	24.3	114.5	70.2	184.7
0099	-41.7	29.4	16.5	66.7	163.3	70.9	234.2
MEAN	-52.2	36.4	65.6	51.1	175.5	101.0	276.5
S.D.	69.7	52.8	60.7	61.7	82.7	95.3	124.7

TABLE A-2 (CONTINUED)

2-3

DEGME: DERMAL TERATOLOGY STUDY IN RABBITS

INDIVIDUAL AND MEAN BODY WEIGHT GAIN VALUES OF PREGNANT RABBITS

DOSE LEVEL: 250 MG/KG/DAY

MATERNAL BODY WEIGHT GAIN (G)

DAY(S) OF GESTATION

ANIMAL NUMBER =====	DAYS 6-9 =====	DAYS 9-12 =====	DAYS 12-15 =====	DAYS 15-19 =====	DAYS 19-29 =====	DAYS 6-19 =====	DAYS 6-29 =====
84A0007	36.1	40.7	-172.6	57.0	162.0	-38.8	123.2
0008	-53.7	13.8	6.5	179.5	255.0	146.1	401.1
0015	174.1	35.0	-185.0	297.0	-21.0	321.1	300.1
0016	-70.2	-95.5	11.5	100.9	75.9	-53.3	22.6
0027	-12.1	39.7	135.0	27.0	321.0	189.6	510.6
0028	26.5	-86.9	232.4	20.8	189.2	192.8	382.0
0035	36.7	37.4	46.9	35.3	156.7	156.3	313.0
0037	1.9	20.4	145.1	20.0	142.0	187.4	329.4
0038	-29.2	-41.0	185.6	50.0	212.3	165.4	377.7
0047	-52.8	10.3	-12.2	16.9	-22.4	-37.8	-60.2
0048	-107.4	-28.7	-83.5	-139.6	125.5	-359.2#	-233.7
0055	-75.5	34.7	98.0	3.4	177.4	60.6	238.0
0067	-13.0	29.9	65.7	82.8	102.5	165.4	267.9
0068	-32.0	-77.4	120.3	-27.3	-22.5	-16.4	-38.9
0075	-57.0	67.9	53.1	114.0	284.6	178.0	462.6
0076	-95.0	40.0	65.0	41.7	243.3	51.7	295.0
0077	-102.5	107.0	5.7	48.9	-267.6	59.1	-208.5
0078	61.0	39.0	41.6	69.4	198.4	211.0	409.4
0087	-6.6	20.5	98.1	36.6	197.4	148.6	346.0
0088	11.7	55.3	95.7	140.4	131.7	303.1	434.8
0089	82.1	67.8	30.9	60.9	148.6	241.7	390.3
0100	-52.0	102.0	44.9	4.9	295.3	99.8	395.1
1994	-36.1	25.5	110.7	64.8	10.0	164.9	174.9
1995	-40.8	4.9	63.9	128.6	44.1	156.6	200.7
MEAN	-16.9	19.3	50.1	59.7	130.8	112.2	243.0
S.D.	64.6	52.4	97.0	80.3	130.7	142.1	207.8

TABLE A-2 (CONTINUED)

2-4

DEGME: DERMAL TERATOLOGY STUDY IN RABBITS

INDIVIDUAL AND MEAN BODY WEIGHT GAIN VALUES OF PREGNANT RABBITS

DOSE LEVEL: 750 MG/KG/DAY

MATERNAL BODY WEIGHT GAIN (G)

DAY(S) OF GESTATION

ANIMAL NUMBER =====	DAYS 6-9 =====	DAYS 9-12 =====	DAYS 12-15 =====	DAYS 15-19 =====	DAYS 19-29 =====	DAYS 6-19 =====	DAYS 6-29 =====
84A0009	47.1	73.0	111.7	-21.3	239.1	210.5	449.6
0010	28.7	-28.6	-132.6	317.8	81.2	185.3	266.5
0017	-64.4	50.9	2.3	62.4	202.0	51.2	253.2
0018	10.2	-96.6	-214.3	-326.7	372.0	-627.4	-255.4
0019	10.0	-94.8	175.4	-77.8	307.4	12.8	320.2
0020	23.2	55.9	110.6	26.0	407.5	215.7	623.2
0029	-26.2	168.5	20.7	123.0	205.0	286.0	491.0
0030	7.1	-82.6	103.1	30.0	374.0	57.6	431.6
0039	-19.0	-64.0	-18.0	113.0	172.7	12.0	184.7
0040	32.2	95.0	40.0	42.2	335.1	209.4	544.5
0049	-25.1	52.5	65.4	-49.4	157.5	43.4	200.9
0057	-52.4	56.9	-94.9	-366.3	578.8	-456.7	122.1
0058	-36.0	34.8	-40.0	-155.8	141.3	-197.0	-55.7
0059	-106.0	-27.6	19.3	107.0	132.8	-7.3	125.5
0070	31.3	-178.7	-262.3	-258.0	-239.9	-667.7	-907.6
0079	-181.3	44.6	42.1	173.4	74.0	78.8	152.8
0080	-13.0	-132.0	65.6	2.6	-8.4	-76.8	-85.2
0091	1.7	-39.3	-22.0	-80.3	17.3	-139.9	-122.6
0092	-44.3	-84.8	-136.2	-340.0	186.0	-605.3	-419.3
1996	-35.9	-39.5	-89.0	-264.0	490.2	-428.4	61.8
1997	-127.0	-207.0	354.9	-21.9	184.0	-1.0	183.0
MEAN	-25.7	-21.1	4.8	-45.9	210.0	-87.8	122.1
S.D.	57.2	95.3	136.8	182.5	183.2	297.1	353.2

----No Data.

#Indicates statistical outliers which are not excluded from calculations.

TABLE A-3

3-1

DEGME: DERMAL TERATOLOGY STUDY IN RABBITS

INDIVIDUAL AND MEAN ORGAN AND BODY WEIGHT VALUES OF PREGNANT RABBITS ON DAY 29

DOSE LEVEL: 0 MG/KG/DAY

ANIMAL NUMBER	BODY WEIGHT (G)	LIVER WEIGHT	
		ABSOLUTE (G)	RELATIVE (G/100G BODY WEIGHT)
=====	=====	=====	=====
84A0001	3868.1	97.55	2.52
0002	4096.1	93.62	2.29
0003	3356.8	102.59	3.06
0004	4321.0	138.64	3.21
0011	4012.0	135.24	3.37
0012	4085.8	97.91	2.40
0021	4253.0	105.31	2.48
0022	3988.4	125.43	3.14
0031	4401.0	115.95	2.63
0032	4714.6	125.50	2.66
0042	4407.9	148.43	3.37
0043	4295.2	88.24	2.05
0044	4750.0	90.81	1.91
0051	4233.0	104.03	2.46
0052	4790.1	119.16	2.49
0061	4254.6	96.40	2.27
0071	3999.2	99.38	2.48
0072	4309.0	111.08	2.58
0081	4139.4	99.93	2.41
0083	4044.0	94.79	2.34
0093	4344.0	110.28	2.54
0095	4643.0	120.19	2.59
0096	3592.0	110.21	3.07
MEAN	4213.0	110.03	2.62
S.D.	344.9	16.22	0.40

TABLE A-3(CONTINUED)

3-2

DEGME: DERMAL TERATOLOGY STUDY IN RABBITS

INDIVIDUAL AND MEAN ORGAN AND BODY WEIGHT VALUES OF PREGNANT RABBITS ON DAY 29

DOSE LEVEL: 50 MG/KG/DAY

ANIMAL NUMBER	BODY WEIGHT (G)	LIVER WEIGHT	
		ABSOLUTE (G)	RELATIVE (G/100G BODY WEIGHT)
=====	=====	=====	=====
84A0005	4084.5	147.51	3.61
0006	3813.0	94.10	2.47
0013	4060.0	109.52	2.70
0014	4443.6	146.13	3.29
0023	4024.0	108.98	2.71
0024	4466.0	129.61	2.90
0026	3893.5	106.25	2.73
0033	4631.0	136.32	2.94
0034	4031.8	131.75	3.27
0045	4248.0	142.06	3.34
0046	4638.4	124.72	2.69
0053	4029.0	119.10	2.96
0054	4472.0	113.45	2.54
0064	4087.8	95.87	2.35
0065	3596.2	86.00	2.39
0066	4263.0	109.56	2.57
0073	4785.5	140.65	2.94
0084	4156.0	127.60	3.07
0085	3898.8	119.52	3.07
0086	3904.0	90.02	2.31
0097	4044.0	98.99	2.45
0098	3962.5	86.46	2.18
0099	3961.0	92.47	2.33
MEAN	4151.9	115.51	2.77
S.D.	296.8	19.85	0.38

TABLE A-3(CONTINUED)

3-3

DEGME: DERMAL TERATOLOGY STUDY IN RABBITS

INDIVIDUAL AND MEAN ORGAN AND BODY WEIGHT VALUES OF PREGNANT RABBITS ON DAY 29

DOSE LEVEL: 250 MG/KG/DAY

ANIMAL NUMBER	BODY WEIGHT (G)	LIVER WEIGHT	
		ABSOLUTE (G)	RELATIVE (G/100G BODY WEIGHT)
=====	=====	=====	=====
84A0007	3702.0	91.05	2.46
0008	4200.0	120.17	2.86
0015	4360.0	111.04	2.55
0016	3921.0	108.13	2.76
0027	4141.0	105.88	2.56
0028	4184.0	102.12	2.44
0035	3913.0	113.27	2.89
0037	4123.0	117.59	2.85
0038	4348.3	142.15	3.27
0047	4457.5	124.86	2.80
0048	3854.7	111.09	2.88
0055	4142.0	120.90	2.92
0067	4760.9	131.31	2.76
0068	3665.0	86.93	2.37
0075	4619.6	156.68	3.39
0076	4500.0	123.19	2.74
0077	4151.0	123.73	2.98
0078	3950.4	96.93	2.45
0087	4161.0	125.23	3.01
0088	4621.8	113.31	2.45
0089	4056.9	92.97	2.29
0100	3977.1	103.30	2.60
1994	4523.0	125.81	2.78
1995	3844.5	89.49	2.33
MEAN	4174.1	114.05	2.72
S.D.	298.6	16.87	0.29

TABLE A-3(CONTINUED)

3-4

DEGME: DERMAL TERATOLOGY STUDY IN RABBITS

INDIVIDUAL AND MEAN ORGAN AND BODY WEIGHT VALUES OF PREGNANT RABBITS ON DAY 29

DOSE LEVEL: 750 MG/KG/DAY

ANIMAL NUMBER	BODY WEIGHT (G)	LIVER WEIGHT	
		ABSOLUTE (G)	RELATIVE (G/100G BODY WEIGHT)
=====	=====	=====	=====
84A0009	4533.5	114.60	2.53
0010	4002.0	115.81	2.89
0017	4144.0	115.51	2.79
0018	3516.0	160.52	4.57#
0019	4206.0	121.01	2.88
0020	4380.0	120.99	2.76
0029	4512.0	185.78	4.12#
0030	4187.0	117.53	2.81
0039	4437.7	135.50	3.05
0040	4727.3	133.42	2.82
0049	4750.0	131.10	2.76
0057	3892.8	105.04	2.70
0058	3664.3	118.20	3.23
0059	4076.8	127.41	3.13
0070	2964.1	68.24	2.30
0079	3980.4	103.94	2.61
0080	3960.8	----	--
0091	4354.0	129.58	2.98
0092	3266.0	74.32	2.28
1996	3841.2	90.28	2.35
1997	4218.0	123.17	2.92
MEAN	4076.9	119.60	2.92
S.D.	454.1	26.03	0.55

----No Data.

#Indicates statistical outliers which are not excluded from calculations.

TABLE A-4

4-1

DEGME: DERMAL TERATOLOGY STUDY IN RABBITS

INDIVIDUAL LITTER SUMMARY OF OBSERVATIONS MADE AT TIME OF CESAREAN SECTION

DOSE LEVEL: 0 MG/KG/DAY

ANIMAL NUMBER	CORPORA LUTEA	IMPLANTS	PRE-IMP LOSS	RESORPTIONS	LITTER SIZE	SEX RATIO (M:F)	BODY WEIGHT (GRAMS)	CROWN-RUMP LENGTH (MM)
=====	=====	=====	=====	=====	=====	=====	=====	=====
84A0001	10	11	0	2	9	4:5	28.5	86.2
0002	8	5	3	0	5	4:1	42.2	91.4
0003	--	9	--	9	0			
0004	14	14	0	1	13	9:4	29.1	83.3
0011	6	6	0	1	5	5:0	46.3	102.4
0012	11	11	0	0	11	5:6	38.9	84.8
0021	10	10	0	1	9	6:3	30.8	86.1
0022	--	1	--	1	0			
0031	8	8	0	0	8	3:5	44.4	89.4
0032	13	11	2	0	11	6:5	37.7	97.4
0042	8	5	3	2	3	2:1	38.0	86.1
0043	9	8	1	1	7	2:5	43.8	91.3
0044	13	13	0	1	12	5:7	40.3	87.5
0051	11	12	0	2	10	6:4	33.0	82.9
0052	9	7	2	2	5	4:1	46.5	94.8
0061	13	12	1	0	12	6:6	31.2	89.0
0071	10	2	8	0	2	1:1	48.5	98.2
0072	9	9	0	0	9	4:5	35.2	87.1
0081	6	5	1	0	5	4:1	38.5	94.1
0082	NON-PREGNANT							
0083	9	10	0	1	9	3:6	39.0	93.7
0093	10	3	7	0	3	3:0	41.0	99.6
0094	NON-PREGNANT							
0095	9	9	0	3	6	3:3	39.4	98.0
0096	11	9	2	2	7	2:5	28.9	89.0
MEAN	9.9	8.3	1.4	1.3	7.0		38.2	91.1
S.D.	2.2	3.5	2.3	1.9	3.8		6.1	5.7

54%:46%



TABLE A-4(CONTINUED)

4-2

DEGME: DERMAL TERATOLOGY STUDY IN RABBITS

INDIVIDUAL LITTER SUMMARY OF OBSERVATIONS MADE AT TIME OF CESAREAN SECTION

DOSE LEVEL: 50 MG/KG/DAY

ANIMAL NUMBER	CORPORA LUTEA	IMPLANTS	PRE-IMP LOSS	RESORPTIONS	LITTER SIZE	SEX RATIO (M:F)	BODY WEIGHT (GRAMS)	CROWN-RUMP LENGTH (MM)
=====	=====	=====	=====	=====	=====	=====	=====	=====
84A0005	12	9	3	3	6	1:5	37.8	92.2
0006	7	8	0	1	7	4:3	33.1	84.1
0013	7	7	0	2	5	3:2	44.1	87.8
0014	10	11	0	2	9	6:3	34.5	87.4
0023	10	10	0	0	10	7:3	39.4	89.7
0024	7	8	0	1	7	3:4	42.7	92.4
0025	FOUND DEAD ON GESTATION DAY 25; PREGNANT							
0026	--	6	--	6	0		----	-----
0033	8	8	0	0	8	5:3	38.9	95.4
0034	7	7	0	2	5	1:4	39.7	98.1
0045	11	10	1	1	9	5:4	38.7	85.3
0046	11	10	1	0	10	6:4	42.2	86.3
0053	12	10	2	0	10	6:4	31.5	89.5
0054	9	9	0	2	7	1:6	39.5	92.6
0064	12	12	0	0	12	5:7	30.1	87.1
0065	14	11	3	0	11	7:4	29.5	85.6
0066	7	7	0	1	6	2:4	45.0	98.0
0073	6	6	0	0	6	4:2	42.1	93.7
0074	NON-PREGNANT							
0084	12	11	1	1	10	3:7	37.2	95.1
0085	8	7	1	0	7	3:4	38.8	85.9
0086	7	7	0	0	7	3:4	38.1	86.4
0097	10	9	1	1	8	4:4	36.8	95.0
0098	8	7	1	1	6	5:1	37.0	85.4
0099	9	9	0	0	9	6:3	30.8	88.1
MEAN	9.3	8.7	0.6	1.0	7.6		37.6	90.0
S.D.	2.3	1.7	1.0	1.4	2.6		4.5	4.4
						51%:49%		

TABLE A-4(CONTINUED)

4-3

DEGME: DERMAL TERATOLOGY STUDY IN RABBITS

INDIVIDUAL LITTER SUMMARY OF OBSERVATIONS MADE AT TIME OF CESAREAN SECTION

DOSE LEVEL: 250 MG/KG/DAY

ANIMAL NUMBER	CORPORA LUTEA	IMPLANTS	PRE-IMP LOSS	RESORPTIONS	LITTER SIZE	SEX RATIO (M:F)	BODY WEIGHT (GRAMS)	CROWN-RUMP LENGTH (MM)
=====	=====	=====	=====	=====	=====	=====	=====	=====
84A0007	11	10	1	1	9	3:6	33.3	89.1
0008	12	12	0	0	12	7:5	34.3	88.2
0015	12	11	1	2	9	5:4	35.5	86.5
0016	11	10	1	1	9	5:4	35.3	92.4
0027	10	9	1	0	9	5:4	39.8	98.7
0028	10	7	3	1	6	1:5	38.5	92.5
0035	10	10	0	0	10	2:8	25.8	80.4
0036	NON-PREGNANT							
0037	10	7	3	0	7	5:2	43.8	101.2
0038	10	10	0	0	10	4:6	37.4	96.3
0047	11	10	1	4	6	3:3	35.6	86.6
0048	8	8	0	0	8	5:3	23.8	76.7
0055	8	7	1	0	7	3:4	34.8	84.4
0067	6	6	0	1	5	1:4	49.4	94.5
0068	8	7	1	0	7	2:5	33.5	84.4
0075	13	11	2	1	10	7:3	29.7	90.8
0076	11	10	1	3	7	4:3	32.8	93.5
0077	--	10	--	10	0	----	----	-----
0078	11	9	2	1	8	4:4	36.0	90.2
0087	13	11	2	0	11	2:9	35.7	95.0
0088	8	8	0	1	7	2:5	36.2	91.8
0089	10	10	0	1	9	3:6	33.0	92.8
0100	10	11	0	0	11	4:7	38.7	94.3
1994	11	10	1	3	7	4:3	26.2	83.5
1995	11	11	0	1	10	5:5	33.2	90.8
MEAN	10.2	9.4	0.9	1.3	8.1		34.9	90.2
S.D.	1.7	1.6	0.9	2.2	2.5		5.5	5.8

44%:56%

TABLE A-4(CONTINUED)

4-4

DEGME: DERMAL TERATOLOGY STUDY IN RABBITS

INDIVIDUAL LITTER SUMMARY OF OBSERVATIONS MADE AT TIME OF CESAREAN SECTION

DOSE LEVEL: 750 MG/KG/DAY

ANIMAL NUMBER	CORPORA LUTEA	IMPLANTS	PRE-IMP LOSS	RESORPTIONS	LITTER SIZE	SEX RATIO (M:F)	BODY WEIGHT (GRAMS)	CROWN-RUMP LENGTH (MM)
=====	=====	=====	=====	=====	=====	=====	=====	=====
84A0009	9	9	0	5	4	2:2	38.5	88.6
0010	9	10	0	1	9	5:4	30.4	77.6
0017	12	10	2	2	8	5:3	30.9	90.4
0018	--	11	--	11	0			
0019	11	10	1	1	9	6:3	36.0	86.3
0020	11	11	0	2	9	5:4	38.9	89.3
0029	5	5	0	0	5	4:1	32.1	78.2
0030	10	2	8	0	2	1:1	41.4	85.7
0039	11	9	2	3	6	3:3	34.0	94.8
0040	12	8	4	4	4	3:1	38.4	97.7
0049	11	8	3	1	7	4:3	38.3	89.4
0050	FOUND DEAD ON GESTATION DAY 20; PREGNANT							
0057	9	8	1	0	8	5:3	28.0	79.9
0058	10	9	1	1	8	4:4	19.7	72.8
0059	11	11	0	9	2	0:2	40.2	91.4
0060	PREGNANT WITH SULFIDE STAIN							
0069	NON-PREGNANT							
0070	--	13	--	13	0			
0079	11	9	2	2	7	2:5	34.6	88.2
0080	11	9	2	2	7	4:3	35.8	89.2
0090	FOUND DEAD ON GESTATION DAY 11; PREGNANT							
0091	12	11	1	1	10	3:7	32.2	81.0
0092	--	8	--	8	0			
1996	10	10	0	2	8	3:5	31.6	94.8
1997	8	8	0	1	7	3:4	36.0	93.9
MEAN	10.2	9.0	1.5	3.3	5.7		34.3	87.2
S.D.	1.7	2.3	2.0	3.8	3.2		5.2	6.8

52%:48%

----No Data.

#### Individual Litter Summary of Fetal Alterations Among Litters of Rabbits

**NUMBER OF FETUSES EXAMINED**

[illegible]

TABLE A-5 (continued)

DFCME: ORAL TERATOLOGY STUDY IN RABBITS

Individual Litter Summary of Fetal Alterations Among Litters of Rabbits

Dose Level: 0 mg/kg/day

NUMBER OF FETUSES EXAMINED

Animal Numbers	8A-0001	0002	0004	0011	0012	0021	0031	0032	0042	0043	0044	0051	0052	0061	0071	0072	0081	0083	0093	0095	0096	Total Fetuses	Total Litters
Vertebrae †	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-thoracic vertebra	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-cervical spur	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-lumbar spur	0	0	0	0	1	0	4	0	0	0	0	0	0	0	0	0	1	0	0	0	2	0	4
-axis, entire site of ossification	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	1
-axis, delayed ossification	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-axis, delayed ossification	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-cervical centra, delayed ossification	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-scapula with fused ribs †	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Ribs †	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-forbed	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-calloused	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-slightly calloused	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-irregular pattern of ossification	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-extra (detached) rib in thoracic area	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Sternum	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-delayed ossification	3	3	8	1	5	7	3	4	6	3	1	5	1	10	1	4	5	5	3	1	0	79	19
-extra site of ossification	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-fused	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	2	2
Other	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-thumb digits, delayed ossification	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

### Individual Litter Summary of Fetal Alterations Among Litters of Rabbits

		Dose Level: 50 mg/kg/day																							
		NUMBER OF FETUSES EXAMINED																							
Animal Number		0005	0006	0013	0014	0023	0024	0033	0036	0045	0046	0053	0054	0064	0065	0066	0073	0084	0085	0086	0097	0098	0099	Total Fetuses	Total Litters
External Examination		6	7	5	9	10	7	8	5	9	10	10	7	12	11	6	6	10	7	7	8	6	9	175	22
Soft Tissue Examination		3	4	3	5	5	4	4	3	5	5	5	4	6	6	3	3	5	4	4	4	3	5	93	22
Skeletal Examination		6	7	5	9	10	7	8	5	9	10	10	7	12	11	6	6	10	7	7	8	6	9	175	22
NUMBER OF FETUSES AFFECTED																									
External Observations																									
-Forelimb flexure - mild†		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	1
-Forelimb flexure - severe†		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-Anomalia		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Soft Tissue Observations																									
-Dilated renal pelvis		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-Retrocaval ureter		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-Convoluted ureter		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-Hydrophrosia and dilated ureter		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-Mineralized deposits in kidney		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-Pale spleen		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	2	2
-Segmented spleen		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-Undersized spleen		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-Accessory spleen		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-Strangulated hepatic teg		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-Hydrocephaly†		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-Undersized left carotid†		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-Ventricular septal defect†		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-Agenesis of gall bladder		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
-Retrosophageal† flight subclavian		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
-Horseshoe kidney		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Skeletal Observations																									
Skull																									
-Hyoid, delayed ossification		3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	5	4	0	0	0	1	19	6
-Hyoid, crooked		0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	2	2
-Parietal bone, delayed ossification		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	1

### Individual Litter Summary of Fetal Alterations Among Litters of Rabbits

NUMBER OF FETUSES EXAMINED

[illegible]

### Individual Litter Summary of Fetal Alterations Among Litters of Rabbits

**Dose Level: 250 mg/kg/day**

**NUMBER OF FETUSES EXAMINED**

[illegible]



### Individual Litter Summary of Fetal Alterations Among Litters of Rabbits

**Dose Level: 250 mg/kg/day**

NUMBER OF FETUSES EXAMINED

[illegible]

TABLE A-5 (Continued)

5-8

## NCCK: DERMAL TERATOLOGY STUDY IN RABBITS

## Individual Litter Summary of Fetal Alterations Among Litters of Rabbits

Dose Level: 750 mg/kg/day

## NUMBER OF FETUSES EXAMINED

Animal Number	0009	0010	0017	0019	0020	0029	0030	0039	0040	0049	0057	0058	0059	0079	0080	0091	1996	1997	Total Fetuses	Total Litters
<b>Vertebrae</b>																				
-hemivertebra †	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	1
-cervical spur	0	1	1	0	2	1	0	0	0	0	0	0	0	0	0	0	0	2	10	6
-lumbar spur	0	0	0	0	1	0	0	0	0	0	0	0	0	1	2	0	0	0	4	3
-axis, extra site of ossification	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-axis, delayed ossification	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	2	2
-axis, delayed ossification	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	1
-cervical centra, delayed ossification	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-scallops with fused ribs †	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1	1
<b>Ribs</b>																				
-forked †	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	1
-calloused	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-slightly calloused	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-irregular pattern of ossification	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-extra (detached) rib in thoracic area	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
<b>Sternum</b>																				
-delayed ossification	3	9	6	9	1	2	2	4	4	6	4	8	2	5	7	10	4	7	93	18
-extra site of ossification	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	1
-fused	1	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	3	3
<b>Other</b>																				
-thumb digits, delayed ossification	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	3	1

† One fetus exhibited ventricular-septal defect, agenesis of gall bladder, retroesophageal right subclavian, and horseshoe kidney.  
 † Considered to be a malformation.

### Individual Litter Summary of Fetal Alterations Among Litters of Rabbits

Dose Level: 750 mg/kg/day

[illegible]

REVIEW OF AN EVALUATION OF DIETHYLENE GLYCOL MONOMETHYL ETHER  
IN PREGNANT RABBITS

E. Marshall Johnson, Ph.D.

March 13, 1985

### Rationale

Diethylene glycol monomethyl ether (DEGME) was applied to the skin of presumed pregnant New Zealand white rabbits (Langshaw Farms, Augusta, MI). The study was conducted in 1984 at the Mammalian and Environmental Toxicology Research Laboratory of Dow Chemical Co., Midland, MI 48640, under the auspices of the Chemical Manufacturers Association. The report is dated 12/10/84 and was a standard Segment II developmental toxicity safety evaluation containing considerations of experimental control and animal husbandry conducive to the generation of sound scientific data capable of being interpreted with confidence.

### Protocol

To begin the study, 100 artificially inseminated rabbits were randomly assigned into four groups. The day of insemination was considered as day 0 of gestation and on this day a lumbar area of approximately 10 x 15 cm was clipped free of hair on each rabbit, and on day 6 an occlusial bandage was applied over this area. Either water or DEGME was inserted under the bandage on days 6-18 of gestation. DEGME was administered at dosages of 0, 50, 250, and 750 mg/kg/day based on results of a preliminary range-finding study. On day 19 the bandages were removed and any residue was wiped away. The females were weighed on days 0, 6, 9, 12, 15, 19 and 29. On day 29 of presumed gestation the females were killed by CO<sub>2</sub> inhalation and the ovaries and uteri were examined, maternal blood was collected for hematologic evaluations, and the maternal liver was weighed.

At autopsy the number of corpora lutea were counted. Also counted were the number of early and late resorption sites, and the number of live and dead fetuses. Half of the live fetuses were randomly selected for soft tissue evaluation via a ventral dissection of unfixed specimens. All fetuses were

fixed in alcohol and then eviscerated and prepared for alizarin red S staining and evaluation of the osseous skeleton.

#### Observations

Maternal toxicity was evident in females treated with 750 mg/kg DEGME. They lost weight during treatment and had reduced red blood cell numbers and packed cell volumes that were lower than those of the other three groups of animals. Maternal weight gain was not depressed in the group receiving 50 mg/kg during any segment of pregnancy. However, from days 9-12, mothers receiving both the 250 and the 750 mg/kg treatment levels gained less than controls or does receiving 50 mg/kg.

At autopsy on day 29 there were 21-24 pregnancies in each of the four groups. There was no affect on the numbers of corpora lutea or implantation sites per dam. From Table 1 it is evident that the number of resorptions per litter, percent implantations resorbed, and percent litters with resorptions were increased in the high dose group, but were unaltered in groups treated with either 50 or 250 mg/kg DEGME.

Fetal crown-rump length was reduced in the high dose group only, though fetal weight appeared slightly lower in the groups receiving both 250 and 750 mg/kg. The fetuses of dams treated with 750 mg/kg DEGME had both a greater variety and greater incidence of numerous developmental alterations. Included among these were forelimb flexure, dilated renal pelvis, altered spleen, delayed ossification, and cervical spurs. Finding of these types, as well as other effects, were present also in fetuses from does receiving 250, 50 and 0 mg/kg DEGME, but without any discernible pattern. Even in the high dose group there was no pattern of effect and the findings reported are those one expects from pregnant rabbits treated at maternally toxic levels. Significantly reduced ossification

was seen (hyoid bone) in fetuses of does treated with 250 mg/kg DEGME. This exposure level also may have increased the incidences of severe forelimb flexure. Incidences of cervical spurs on a fetal and litter basis in the 0, 50, 250 and 750 mg/kg dose groups were 0, 2, 9, 8, and 0, 14, 35 and 33 percent, respectively.

#### CONCLUSIONS:

##### Maternal

Pregnant rabbits dermally exposed to 750 mg/kg of DEGME from days 6-18 of gestation showed overt signs of toxicity evidenced as weight loss and reduced red blood cell numbers. At a dosage of 250 mg/kg maternal effects were absent though weight gain between days 9 and 12 may have been depressed. Dermal exposure to 50 mg/kg DEGME had no effect on any of the numerous maternal parameters measured.

##### Developmental

Marked developmental toxicity was produced by the severely maternally toxic exposure level of 750 mg/kg. It was evident as an increased incidence and variety of developmental variations. At a treatment level of 250 mg/kg fetal body weight was less than controls, hyoid ossification was generally retarded, and several cervical spurs were present. The exposure level of 50 mg/kg had no marked affect on any developmental parameter. Fetal weight and hyoid ossification were not affected. Incidences of cervical spurs were greater than the concurrent controls and may have occurred in these fetuses at a greater frequency than in pooled historic controls. In my view, cervical spurs do not constitute a major malformation and in this study they did not occur in a dose-related manner.

##### Conclusions

It is my considered opinion that 50 mg/kg DEGME is a clear and obvious

NOEL for both maternal and developmental toxicity. Furthermore, even at exposure levels high enough to severely affect the mothers, there was no pattern of malformation produced by DEGME. The developmental effects seen are in the nature of those one expects from compromised mothers. The data available indicate that (1) DEGME is not a primary teratogenic hazard, and (2) developmental effects are evident only in conjunction with maternal toxicity.

#### Summary

Diethylene glycol monomethyl ether (DEGME) has been examined in a standard developmental toxicity safety evaluation. Cutaneous application of DEGME at high levels produced overt maternal toxicity and an increased incidence and variety of developmental variation. Exposure to 50 mg/kg/day in this study is considered to be the NOEL for both maternal and developmental effects.



Table 1

Effect of DEGME on Selected Developmental Parameters

	<u>Treatment Groups (mg/kg/da)</u>			
	<u>0</u>	<u>50</u>	<u>250</u>	<u>750</u>
# resorptions/litter	1.3 $\pm$ 1.9	1.0 $\pm$ 1.4	1.3 $\pm$ 2.2	3.3 $\pm$ 3.8
% implants resorbed	15	12	14	37
% litters w/resorptions	61	57	58	86
fetal weight (g)	38.2 $\pm$ 6.1	37.6 $\pm$ 4.5	34.9 $\pm$ 5.5	34.3 $\pm$ 5.2
fetal C-R length (mm)	91.1 $\pm$ 5.7	90.0 $\pm$ 4.4	90.2 $\pm$ 5.8	87.2 $\pm$ 6.8



DOW CHEMICAL U.S.A.

January 15, 1985

MIDLAND, MICHIGAN 48640

Dr. Lori Ramonas  
Glycol Ethers Administrator  
CMA  
2501 M Street N.W.  
Washington, D.C. 20037

For Distribution by CMA  
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From L. Ramonas  
Ref. No. G-E Paper-T-12TG  
Date 1-23-85

Dear Lori;

Enclosed are 10 copies of a draft manuscript for the DEGME 90-day vapor inhalation study which we would like to submit for publication in Fundamental and Applied Toxicology. We have had numerous inquiries about the results of this study, and I think it would be highly desirable to get the manuscript published if possible. Please distribute the manuscript to the sponsors for their review. If we do not hear anything by February 4, 1985, we will submit the manuscript for publication in its present form.

Sincerely,

*R. R. Miller*

R. R. Miller, Ph.D.  
Mammalian and Environmental Toxicology  
Research Laboratory  
1803 Building  
(517) 636-2584

ej

Enclosures

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JAN 25 1985

T. R. TYLER, Ph. D.





UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

William C. Kuryla, Ph.D.  
Associate Director, Product Safety  
Union Carbide Corporation  
39 Old Ridgebury Road  
Danbury, Connecticut 06817-0001

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PREVENTION, PESTICIDES AND  
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MAY 08 1995

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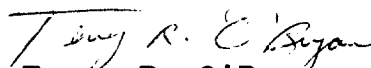
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Sincerely,

  
Terry R. O'Bryan  
Risk Analysis Branch

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SUBMITTER NAME: Union Carbide Corporation

INFORMATION REQUESTED: FLWP DATE:  
0501 NO INFO REQUESTED  
0502 INFO REQUESTED (TECH)  
0503 INFO REQUESTED (VOL ACTIONS)  
0504 INFO REQUESTED (REPORTING RATIONALE)  
DISPOSITION:  
0639 REFER TO CHEMICAL SCREENING  
0678 CAP NOTICE

VOLUNTARY ACTIONS:  
0401 NO ACTION REPORTED  
0402 STUDIES PLANNED/UNDERWAY  
0403 NOTIFICATION OF WORKING CONDITIONS  
0404 LABEL/MSDS CHANGES  
0405 PROCESS/HANDLING CHANGES  
0406 APP. USE DISCONTINUED  
0407 PRODUCTION DISCONTINUED  
0408 CONFIDENTIAL

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CHEMICAL NAME:

CAS#

111-77-3

INFORMATION TYPE

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0201	ONCO (HUMAN)	01 02 04
0202	ONCO (ANIMAL)	01 02 04
0203	CELL TRANS (IN VITRO)	01 02 04
0204	MUTA (IN VITRO)	01 02 04
0205	MUTA (IN VIVO)	01 02 04
0206	REPRO/TERATO (HUMAN)	01 02 04
<u>0207</u>	REPRO/TERATO (ANIMAL)	01 02 04
0208	NEURO (HUMAN)	01 02 04
0209	NEURO (ANIMAL)	01 02 04
0210	ACUTE TOX. (HUMAN)	01 02 04
0211	CHR. TOX. (HUMAN)	01 02 04
0212	ACUTE TOX. (ANIMAL)	01 02 04
0213	SUB ACUTE TOX (ANIMAL)	01 02 04
0214	SUB CHRONIC TOX (ANIMAL)	01 02 04
0215	CHRONIC TOX (ANIMAL)	01 02 04

INFORMATION TYPE:

P F C

0216	EPI/CLIN	01 02 04
0217	HUMAN EXPOS (PROD CONTAM)	01 02 04
0218	HUMAN EXPOS (ACCIDENTAL)	01 02 04
0219	HUMAN EXPOS (MONITORING)	01 02 04
0220	ECO/AQUA TOX	01 02 04
0221	ENV. OCC/REL/FATE	01 02 04
0222	EMER INCI OF ENV CONTAM	01 02 04
0223	RESPONSE REQUEST DELAY	01 02 04
0224	PROD/COMP/CHEM ID	01 02 04
0225	REPORTING RATIONALE	01 02 04
0226	CONFIDENTIAL	01 02 04
0227	ALLERG (HUMAN)	01 02 04
0228	ALLERG (ANIMAL)	01 02 04
0239	METAB/PHARMACO (ANIMAL)	01 02 04
0240	METAB/PHARMACO (HUMAN)	01 02 04

INFORMATION TYPE:

P F C

0241	IMMUNO (ANIMAL)	01 02 04
0242	IMMUNO (HUMAN)	01 02 04
<u>0243</u>	CHEM/PHYS PROP	01 02 04
0244	CLASTO (IN VITRO)	01 02 04
0245	CLASTO (ANIMAL)	01 02 04
0246	CLASTO (HUMAN)	01 02 04
0247	DNA DAM/REPAIR	01 02 04
<u>0248</u>	PROD/USE/PROC	01 02 04
0251	MSDS	01 02 04
0299	OTHER	01 02 04

TRIAGE DATA: NON-CBI INVENTORY

YES

CAS SR

NO

IN TERMINI

ONGOING REVIEW

YES (DROP/REFER)

NO (CONTINUE)

REFER

SPECIES

RBT

TOXICOLOGICAL CONCERN:

LOW - MOD

MED

HIGH

USE:

solvent

PRODUCTION:

COMMENTS

Dermal Teratology - Rabbits (DEGME)  
0, 50, 250, 750 mg/kg/d GD 6-18

at 750 mg/kg/d: Slight embryotoxicity  
feto- and maternal toxicity.  
Delayed ossification, ↓ maternal  
body wt gain, ↓ RBC & PCV values  
slight ↑ resorption  
Slight fetotoxic - delayed ossification at 250  
No effects at 50 mg/kg/d